| Use Case | Description | Other Possible Technologies Required | Samples | Comments |
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| 1. Triage of symptomatic individuals in an epidemic setting | * The intended use is to determine if a symptomatic individual in an epidemic setting has a reasonable likelihood of a current infection warranting temporary isolation pending confirmatory testing * Target use settings can be divided into two groups:   + Group 1: Sites with temporary (days) or fulltime residents such as assisted living centers, cruise ships, hospitals and quarantine facilities.   + Group 2: Settings could include public and community health centers, primary care facilities, urgent care clinics, and emergency departments in outbreak areas where symptomatic individuals could be expected to visit for work-up. | * If nasal or nasopharyngeal swabs are required, proper collection (e.g., swab) and sample introduction to testing device (e.g., swab introduction port) will be necessary * Typically, a confirmatory test using different targets is needed, unless triage test clinical performance is very high * It is possible that home self-tests will be deployed for triage — where positive results are not diagnostic, but will indicate that the individual should go to an appropriate confirmatory testing center or care facility * Information and communications technologies (ICT) to capture and report data for reporting to other stakeholders is needed (e.g. healthcare workers, MOH, Public Health, CDC, WHO). If a differential diagnostic test is performed, in addition to a confirmatory test, association of the triage test data with these diagnostic test results is desirable. | * At the time of writing (March 25, 2020) the preferred sample type is still under investigation, though nasal and nasopharyngeal swabs remain common choices * Other potential sample types used by some laboratories and test developers for SARS-CoV-2 include oral fluid, bronchial lavage, sputum, blood, urine and feces * It may not be practical to obtain and process all sample types in all settings. “Sample-to-results” procedures should be carefully considered and matched to the end user capabilities. * For self-tests, sample collection with oral fluid or finger prick blood are preferred if possible since proper self-collection with a nasal swab could be difficult | * The turnaround time should be maximally 1 hour, preferably 15 minutes or less * The potential use of a triage test in an epidemic setting is tied to the availability of an acceptable confirmation test. Confirmatory testing solutions and algorithms appropriate for the intended use setting should be recommended. * Confirmation testing will not always be available at the site of triage testing. In this situation, it could necessary for the individual to be isolated near the site of testing or at home until confirmation send-out test results are obtained. * The intended use settings can be roughly divided into two groups with different testing requirements.   + In Group 1 sites, individuals can likely be isolated and confirmation testing can be conducted remotely (multi-day send out);   + In Group 2 sites, remote confirmation testing is more problematic unless it can be conducted on site and rapidly. With send out testing it will not be possible to keep patients on site long enough to isolate them to prevent potential transmissions. * A triage test that permits the majority of symptomatic patients to leave if they have a negative result (low probability of SARS CoV-2 infection; high sensitivity, high negative predictive value) would limit the need to isolate and test for confirmation of infection. * On the other hand, the test requires an acceptable specificity so that few people are unnecessarily quarantined. Even in an epidemic setting it is likely that most persons with symptoms do not have COVID-19. * In most of the intended use settings, a point of care (POC) format test is desirable, ideally one that is designed to meet CLIA-waiver requirements. While an instrument-free format has merit in many target use settings, the desire to capture and communicate information as well as features delivering improved test performance may favor automated solutions. * Tests designed for decentralized POC testing should take into account the requirements across the wide variety of potential testing locations, environments, operators and regulatory requirements. * It is likely that medical practitioners and technical staff in the target use settings will be wearing some form of personal protective equipment (PPE), which has implications for the type of sample that can be obtained (e.g., finger prick blood or nasal swabs while wearing gloves), how it can be processed (e.g., micro-capillary manipulation observation while wearing a mask) and the operator interfaces on the devices used (e.g., sample addition and touch screen while wearing gloves). * Price targets\* (to the end user) are likely to be <$25 USD for the US, but considerably less in low and middle-income countries (LMICs). * Frequently in high income countries (HIC), established reimbursement is dependent on the type of assay technology used. |
| 1. Triage of symptomatic individuals in endemic settings | * The intended use is to determine if a symptomatic individual in an endemic setting has a reasonable likelihood of a current infection warranting temporary isolation pending confirmatory testing * Intended use settings include both Groups 1 and 2 from Use Case 1, as well as all other sites where individuals could present seeking primary care | * Same as above | * Other potential sample types probably would not include bronchial lavage, sputum or feces | * This scenario assumes the virus will remain a recurring threat, requiring ongoing potential testing of individuals presenting with respiratory symptoms. Note: this comment is pertinent to all the remaining Use Cases * The disappearance of SARS-CoV-2 from the local population could be due to the seasonal nature of the disease or effective elimination followed by reintroduction * Most individuals presenting with symptoms under this scenario are less likely to be infected with SARS-CoV-2 than in the epidemic setting scenario. Common cold, flu, seasonal allergies or febrile diseases with similar clinical presentations will be more common, creating the potential need for confirmatory testing and/or differential diagnostics. * The turnaround time should be maximally 1 hour, preferably 15 minutes or less * The need for high sensitivity remains, but in this scenario, there is also the need for higher specificity since in a low prevalence environment the majority of individuals could be false positives. * In these use settings, isolation will become a major annoyance and a likely impediment to testing. Therefore, is it important that confirmation testing be rapid, preferably offered at the site of triage testing. * It is possible that triage testing will not be ideal in some endemic settings where diagnostic tests (Use Case 5) would offer a more appropriate testing solution. * For broadest utility, it is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings. * Price targets are likely to be less than for the epidemic scenario Use Case, <$15 USD in the US, but considerably less in LMICs. |
| 1. Triage of at-risk pre-symptomatic and symptomatic individuals in endemic settings | * The intended use is to determine if an at-risk individual with or without symptoms in an endemic setting has a reasonable likelihood of a current infection warranting temporary isolation pending confirmation testing. | * Same as above | * Same as Use Case 2 | * While the sites for testing under this scenario are the same as for Use Cases 1 and 2, testing for pre-symptomatic individuals is far more difficult. Testing of the general population is problematic for a variety of reasons, including cost, access, awareness, appropriateness, logistics and others. * This scenario could include pre-symptomatic, at-risk contacts of individuals who tested positive for SARS-CoV-2. * Alternatively, sentinel populations (e.g., nurses, doctors, first responders) could be established and monitored at their site of work. * In an endemic setting, a new symptomatic case(s) will occasionally appear and could initiate a broader testing protocol for recent contacts. * Decentralized testing is a preferred option for rapid turnaround, prevention of loss to follow-up and other reasons. * In this case, using tests with very high sensitivity and specificity (>99%) could reduce or eliminate the need for confirmation testing. Individuals testing positive would be moved immediately to isolation or quarantine. The large majority of individuals will be negative for COVID-19 (likely >99%). Such a triage test would be virtually indistinguishable from a diagnostic test in terms of performance, with the possible exception of cost and ease of use factors. * The turnaround time should be maximally 1 hour, preferably 15 minutes or less. * For broadest utility, it is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings * Price targets are likely to be <$25 USD in the US since there would be premium value for identifying individuals early, and for convenience, but pricing pressure would remain in LMICs. |
| 1. Confirmatory testing | * The intended use is to confirm that an individual is currently infected with SARS-CoV-2 after triage testing * Sites of testing would depend on where the triage tests are being performed. In some situations, confirmation testing will be conducted at the same site as triage testing (same day), while in others testing could be a send-out test (multi-day) | * Same as above | * Sample types may be restricted to those validated for use with the highest performing assay technologies. * Samples for confirmation testing could be different than for the triage test. * It could be useful to have self-collection of samples with either courier pick up or shipment to testing sites for confirmation | * It will be important to consider whether or not sufficient sample should be taken at the time of triage testing for potential use with a confirmatory test (if warranted), or if a second sample is collected after results are obtained for triage tests. Taking a new second sample will be far easier in Group 1 sites than Group 2 sites (see Use Case 1) unless the confirmation test is available at the Group 2 site. * In Group 2 sites, local confirmation testing is preferred, for instance, in a qualified lab near an emergency room or primary care facility. * In Group 2 sites without local confirmation testing, it is probable that an individual will go home to self-quarantine after a positive triage test. In this case additional sample collection would be required if the confirmatory test is a send out. * The potential for loss to follow-up must be considered in the case of the Group 2 sites. * On site turnaround of results <2 hours is preferred, but sooner would be better * If send-out testing is required, delayed delivery of test results (several days) could result in unnecessary isolation/quarantine. * It is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings, or CLIA moderately complex for use by laboratorians in small laboratories. * If the triage testing is performed in settings with minimally trained personnel, careful thought should be given as to whether the confirmatory test should require a higher level of training or should be designed to accommodate sites with only minimally trained personnel available. * Sensitivity and specificity targets are less stringent than for a diagnostic test, since after triage testing the population should be greatly enriched for infected persons. * In instances where the triage test has high enough performance, or when a diagnostic test is used for triage, the confirmatory test may not be required. * Price targets are less stringent here where pricing could be up to $100 USD; lower in LMICs. |
| 1. Diagnosis of symptomatic individuals in endemic or epidemic settings | * The intended use is to diagnose a symptomatic individual with a SARS CoV-2 infection in an epidemic or endemic setting * Sites include locations where individuals commonly present seeking primary care, such as emergency rooms, urgent care clinics, hospitals and primary healthcare facilities or where individuals are referred for advanced care | * Same as above | * Same as Use Case 1, except for self-testing. * It could be useful to have self-collection of samples with either courier pick up or shipment to testing sites for testing could be useful | * Sensitivity and specificity will need to be quite high (> 99%). A false negative result, particularly in elderly or immunocompromised individuals, could result in a high morbidity and mortality rate, while also increasing the risk to medical personnel and increasing transmission. * The performance of a confirmation test can be far below that of a diagnostic test because after triaging test the population will be greatly enriched for positive cases prior to confirmation. In contrast, the diagnostic test is used in a much broader population based on symptoms only. For instance, in a low prevalence setting of 0.1% the diagnostic test with a specificity of 99% would yield 10 false positive results to 1 true positive result. On the other hand, if in the same population had been enriched by 100-fold during triage testing, a confirmation test with a 99% specificity would be acceptable. * False positives would lead to unnecessary and costly quarantine or hospitalization. Also, healthcare personnel might be forced to wear extra PPE when it is not needed. * Cross-reactivity with other respiratory and febrile pathogens and/or interfering substances would be highly problematic. * The turnaround time should be maximally 1 hour, ideally 15 minutes or less. * If off-site, send-out testing is required, delayed delivery of test results (several days) could impact the likely outcome of the person tested or result in unnecessary isolation/quarantine. * A test designed to meet the requirements for use in an endemic setting is also likely to meet the demands for an epidemic setting. One possible exception is the use of PPE, which is less likely to be encountered in an endemic setting than in an epidemic setting. If the diagnostic test is intended for use in both settings, consideration should be given to operator interface requirements for individuals wearing PPE. * It is preferable that the test be CLIA-waivable for use by minimally trained users in decentralized testing settings, or CLIA moderately complex for use by laboratorians in small laboratories. * Price targets for a robust test could be up to $30 USD. Less in LMICs. |
| 1. Differential diagnosis in endemic or epidemic settings | * The intended use is to diagnose an individual with influenza like illness (e.g., Flu A, Flu B, RSV, SARS-CoV-2) in an endemic or epidemic setting * It could be useful to also add common febrile disease pathogens, given the early clinical presentation of some COVID-19 patients (e.g., fever, aches, no respiratory symptoms) * Differential diagnosis could be applied in Use Cases 1, 2, 3, and 5 * For use at the first healthcare site a patient or their contacts would enter to receive treatment * A positive test for SARS-CoV-2 or other epidemic-associated pathogens could trigger extra precautions, such as quarantine, confirmatory testing, additional PPE, and contact follow-up, including healthcare staff | * Same as above * For differential diagnostics, sample preparation can be a key challenge. For example, pathogens that present in very low concentrations in the target sample may require additional steps such as culture, larger sample volumes, sample concentration, or other processes. * Could be important to include additional pathogens to the test. See comments. | * Sampling of the upper respiratory tract alone may not be a sufficient sample source for a differential diagnostic since the optimum sample for one pathogen could be different for others. As a result, careful consideration must be given to appropriate samples and sample preparation requirements. * Multiple sample types could be required. * It could be useful to have self-collection of samples with either courier pick up or shipment to testing sites for testing could be useful | * Most of the individuals presenting to healthcare facilities with symptoms of respiratory or febrile disease illness are unlikely to have contracted COVID-19, even in epidemic settings. Possible exceptions could include elderly individuals from assisted living facilities or other close human contact settings with known infections. * Detection of other potential causative agents could provide healthcare workers with an immediate opportunity to treat and thus avoid further work up and postponement of treatment. * Multiple pathogens could be present when viral infection leads to bacterial pneumonia or sepsis. * If the test is designed to meet the higher performance requirements for endemic settings it should also be useful in epidemic settings with lower performance requirements. * Determining whether upper or lower respiratory pathogens are indicated for testing is a critical consideration. For upper respiratory infections, the test optimally would include the 4 coronaviruses associated with the upper respiratory infections and the common cold (HCoV 229E, NL63, OC43 and HKU1), plus influenza A and influenza B. Depending on the region, time of year, and setting, other common respiratory pathogens might also be considered, such as RSV. Lower respiratory targets would include bacteria associated with pneumonia, bronchitis and potentially tuberculosis. * Pathogens of febrile disease present more of a challenge based upon the geographic location of testing. * A single multiplex test designed to detect multiple pathogens from a single sample, or multiple tests (aka multi-parallel format), would be required. Multiple tests could be required to deal with multiple sample types needed. * By referring either the sample or the patient for testing to other facilities, the test could be deployed at higher level infrastructure facilities to diagnose cases not possible to detect with existing technologies available at lower level centers; PPE use could vary from site to site. * There could be additional clinical benefits to knowing that SARS-CoV-2 is a co-infection with other respiratory or febrile disease-causing pathogens, including shortened time to treatment, reduced risk of complications, reduction in health system crowding and reduced risk of disease transmission. * There is a substantial challenge to developers to create multiplexed or multi-parallel tests with the necessary and sufficient performance for each target and, for multiplex tests, using a common sample type and sample preparation method. * It is possible that in some situations it would be more useful to test for more common respiratory and febrile disease pathogens first, and then follow up with a differential diagnostic for other pathogens when a simpler cause was not found. * A confirmatory test for all targets is not practical or necessary. * If none of the pathogen targets of the differential diagnostic test are detected, it could be important to test for outbreak pathogens with major population health implications, such as Lassa, Marburg, Ebola, SARS-CoV and MERS-CoV. * Bio-Threat pathogens are not considered here. * Typically, instituting panel tests is cost prohibitive, although reports of inexpensive alternatives have appeared. * In the event that there is a triage or disease severity test available that didn’t correlate with a specific pathogen (e.g., procalcitonin), then performing the differential diagnostic test could be quite useful. * Price targets are somewhat higher than for a diagnostic test, in the $30-$120 USD range, depending on the number of targets included and the assay technology used. Less in LMICs. |
| 1. Previous SARS-CoV-2 exposure | * Intended for use to determine if an individual without symptoms has previously been exposed to SARS-CoV-2. * If the clinical data supports the claims, such an individual would not require quarantining and could associate with uninfected or infected individuals with minimal danger of transmission or new infection. | * Probably in a simple LFA or similar RDT format. * If necessary, could be performed with an ELISA or similar test format in a lab setting. * If antibody titer is required, the test would need to be quantitative | * Likely to be blood, preferably finger prick. * For an ELISA test, venipuncture blood could be collected and shipped. * Oral fluid is an alternative if antibody concentrations are high enough but would not be useful if a quantitative result is required. | * The test could be a simple SARS-CoV-2 specific IgG detection assay. * Determining recency of infection could be helpful in determining whether an individual was previously infected with SARS-CoV-2 (e.g., IgM). * Given recent reports of potential transmission of the virus many days after apparent COVID-19 cure, it is possible that a viral clearance test will be necessary in conjunction with an antibody test to determine that the infection has been resolved * If possible, it would be quite valuable to use the test to assess protective immunity * If immunity is temporary and the antibody clears after a few months, it might be necessary to measure the antibody titer. This approach would require that the effective titer is not too variable from person to person. * IgG to specific antigens could be indicative of immunity (e.g., nucleocapsid or spike protein) while other antigens are not. * It is conceivable that it will be necessary to assess IgG subclasses. * It could be necessary to develop viral neutralization/inhibition assays to confirm immunity (e.g., *in vitro* vero cell screening with SARS-CoV-2 cultures and patient samples). * In the event that quantification of antibodies will be necessary, the ELISA (or equivalent) format is probably easier to develop than a quantitative LFA or similar RDT. * It could be useful to conduct serology studies in a cohort of cured patients to monitor antibody titers and immunity over time. * Once vaccines are developed and widely used, there could become challenges to differentiating natural immunity from successful vaccination. |
| 1. Surveillance in sites of previous or potential outbreaks | * Intended use is to monitor a local or sentinel population in order to obtain early indications of a COVID-19 outbreak. * If SARS-CoV-2 diagnostics are not in routine use in the location of interest, procedures to test a statistically meaningful subset of the respiratory and febrile disease patient populations would be used. * In most situations, samples from a subset of the respiratory and febrile disease patients or healthcare workers in sentinel clinics would be sent for testing at a remote site. * Positive confirmation would trigger a planned response. * The test would not be used for a “test and treat” approach. | * Use of multiplex assay technologies designed to detect more than one pathogen can be a convenient means of surveillance, provided test utility, ease of use, and cost, match the target requirements. * It is conceivable that batching of samples will be necessary to achieve cost goals. * Molecular labeling (e.g., “bar coding”) of individual samples, in order to combine them for subsequent PCR or NGS analysis followed by de-convolution, could be used. * Remote, safe collection, and transport of samples under safe conditions is required. * A confirmatory test using different targets could be needed, depending on the configuration of the primary test (e.g., multiple viral target genes). * ICT is needed for communication of results to stakeholders (e.g. healthcare workers, local governments, MOH, Public Health, CDC, WHO). | * The test must be developed to work with samples that are conveniently collected, such as nasal swabs, nasopharyngeal swabs, and blood. * Feces is a possible alternative. * Stabilization and deactivation of samples prior to safe shipment could be important. | * If SARS-CoV-2 infection diagnostic testing becomes a routine part of respiratory and febrile disease diagnosis in endemic settings, a new surveillance test might not be necessary, only ICT is needed to report results in real time. * If SARS-CoV-2 diagnostics are not routine, the determination of a new outbreak would require surveillance of some portion of the respiratory and febrile disease population, with the statistical sampling size to be determined. * NGS methods are attractive for surveillance, but RNA, antigen and/or antibody (IgM) detection could be an alternative. Unfortunately, so far the virus has not been routinely detected in blood. NGS would provide additional information concerning the genetic variation in SARS-CoV-2 over time and location. * Turnaround time is important, but not critical; it is far more critical that “hits” (putative positives) are real; a protocol using additional tests to certify that hits are true positives could be important, depending upon the clinical performance of the surveillance test. * Specificity will be a significant issue, but it is possible that confirmation assays could be used after a hit, preferably to detect a different viral target molecule (e.g., gene or antigen). * Sensitivity is also critical to avoid false negative results * It is not necessary to test all samples independently, but it is highly desirable to know which person in a pooled batch was infected; molecular labeling methods could make this approach economically feasible. * ICT systems to alert key stakeholders, coupled to a planned response, would be essential. |
| 1. Environmental monitoring | * The intended use is to monitor for the presence of SARS-CoV-2 on surfaces, in the air, in latrines or other sites of interest. * Could be used in healthcare, residential, businesses and other places of crowded occupation. | * Sample collection, transport, elution, purification, concentration and other sample preparation steps are likely to be highly variable. * Technology that collects and preserves target molecules will be required. * It is possible that tests of viral RNA, protein or other components might not correlate with infectivity. Therefore, additional information could be required (e.g., intact RNA versus fragments). | * Given the potentially diverse sample types, collection devices and procedures, sample preparation methods can be quite different from other Use Cases. * Consideration should be given to how various sample collection media, sample and target analyte handling, transportation, storage, and stability considerations are handled. * It is possible that many samples can be combined to decrease cost. | * This test could be used as an aid in validating contaminated area cleaning procedures or for general monitoring. * Test results could be used to verify that sites where people gather are free of SARS-CoV-2 contamination: healthcare facilities, assisted living sites, residential areas, food vendors, schools, places of business, restaurants, hotels, sports facilities, food preparation companies, prisons, coffee shops, airplanes, and others. * Cost targets would need to be quite low for any routine monitoring use, and higher for infrequent verification or process validation use. * Operator interface steps must be carefully considered. * It is essential that test results are meaningful. It is possible that many reports to date of long virus persistence on surfaces and in cruise ship living quarters will not correlate with the viral materials tested being capable of actual transmission (e.g., virus not intact). The test would be most valuable if the results could be compared to the *in vitro* infectivity of the isolated virus-derived samples. This requirement for detecting infectivity will be a challenge for sample collection, preservation, and preparation to conduct the *in vitro* infectivity testing. |

\*Price targets refers to the target price to the end user. This is a highly variable target, depending on the target use setting. Payments and reimbursement amounts are frequently influenced by the type of assay technology used. This may not be the complete price per result if other ancillary equipment or consumables are required. For health economic modeling, the complete price per result must be considered.